HIV vaccine-induced antibody responses impacts the accuracy of HIV testing algorithms in sub-Saharan Africa

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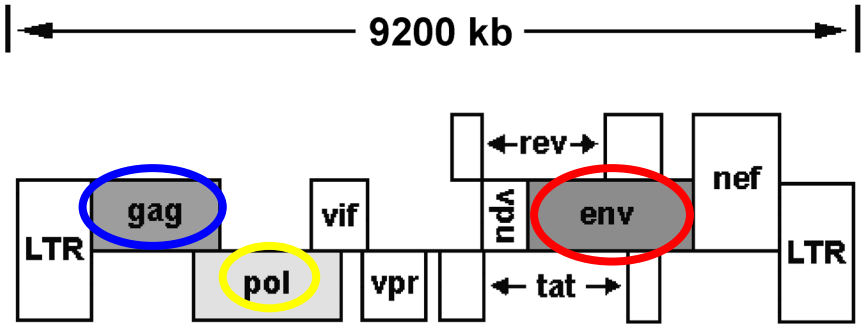
Introduction

- A series of clinical HIV phase I/II vaccine trials were conducted in Sweden, Tanzania and Mozambique 2005 to 2015

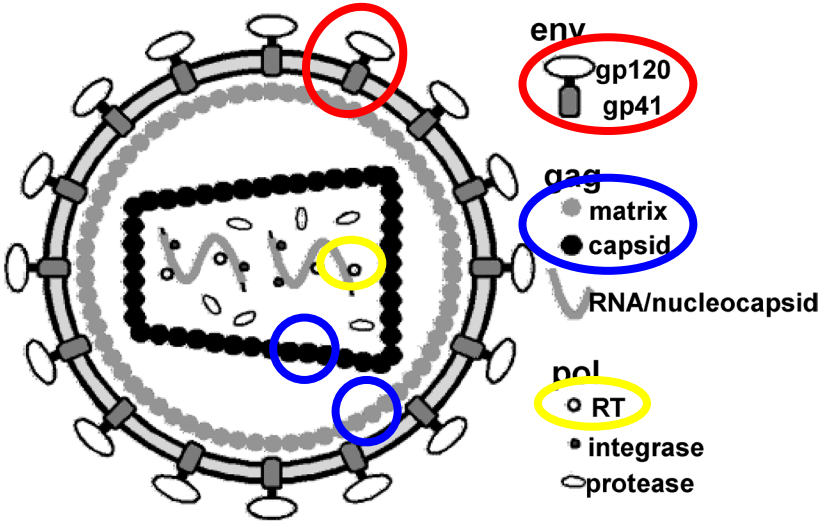
- Prime-boost vaccine strategy using DNA-MVA-protein vaccines

Introduction

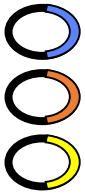
DNA-MVA-protein vaccine



HIV-1 genome



HIVIS-DNA



Env subtyp A,B,C

Gag subtyp A,B

Rtmut

rev B

HIVIS-DNA KI Wahren et al Mol Ther 2007;15:1724–1733

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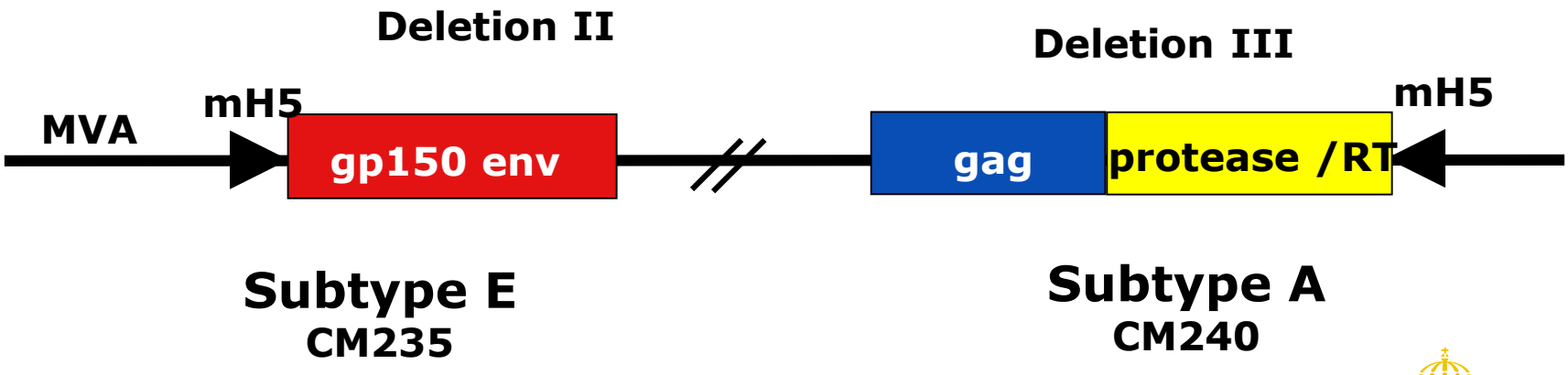
Introduction

DNA-MVA-protein vaccine

Modified Vaccinia virus Ankara (MVA)/ Chiang Mai Double Recombinant (CMDR)

Developed by P Earl and B Moss, Laboratory of Viral Diseases, NIAID, NIH
Produced by Walter Reed Army Institute of Research



HIV-MVA-CMDR NIH/WRAIR Earl et al Vaccine 2009;27:5885–5895.

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Introduction

DNA-MVA-protein vaccine

- is a recombinant subtype C HIV-1 gp140 Env glycoprotein, CN54rgp140 adjuvanted with GLA-AF.

- GLA-AF is an adjuvant containing an aqueous formulation of glucopyranosyl lipid A, which is a synthetic monophosphoryl lipid A (MPL)-like molecule

Clegg CH, et al GLA-AF, an emulsion-free vaccine adjuvant for pandemic influenza. PLoS One. 2014; 9(2):e88979

Introduction

HIVIS01/02/05 phase I trial (3 HIV-DNA+2 HIV-MVA)

- All (100%) of 24 vaccinees developed antibodies to GAG
- All (100%) of 24 vaccinees were reactive in IMvHIV-1/HIV-2 III plus (Abbott) ELISA
- 13 (54%) of 24 were reactive in Enzygnost HIV Integral II ELISA
- 13 (54%) of 24 were also reactive in Western Blot (CDC criteria for positive classification; at least two bands of p24, gp41 or gp120/160)

Nilsson C, et al. AIDS Res Hum Retroviruses 2014

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Introduction

- Healthy uninfected HIV vaccine recipients will develop antibody responses that may result in diagnostic immunoassay reactivity, also known as vaccine-induced seroreactivity (VISR)
- HIV DNA or RNA PCR is used in all clinical HIV vaccine trials to rule out infection
- Volunteers in HIV vaccine trials carry a card identifying them as HIV vaccinees

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Introduction

HIV diagnosis in resource–restricted countries depend on rapid diagnostic tests (RDTs)

	Determine HIV1/2	SD Bioline HIV1/2 3.0	Uni-Gold™ HIV-1/2
			
	15 min	10-20 min	10 min
Antigens:	HIV-1 and HIV-2 Recombinant protein (RP) and synthetic peptide	Recombinant HIV-1 gp41, p24 HIV-2 p36	HIV-1 gp41, gp120 RP HIV-2 p36 RP
Antibodies:	IgG	All isotypes	IgG

Introduction

HIV diagnosis in resource–restricted countries depend on rapid diagnostic tests (RDTs)

The HIV diagnostic algorithm used in Tanzania

Sequential testing using two RDTs

1. SD Bioline HIV1/2

Reactivity in the 1st RDT is confirmed by a 2nd RDT

2. Uni-Gold™ HIV-1/2

→ Linkage to treatment and care

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Introduction

The HIV diagnostic algorithm used in Mozambique

Sequential testing using two RDTs

1. Alere Determine HIV1/2

Reactive

2 lines of any intensity appear in both the control and patient areas.

Reactivity in the 1st RDT is confirmed by a 2nd RDT

2. Uni-Gold™ HIV

Reactive

2 lines of any intensity appear in both the control and test areas.

→ Linkage to treatment and care

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Objective

- To explore the impact of VISR on the performance of HIV rapid diagnostic tests and to evaluated two African countries' HIV diagnostic algorithms

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Material and methods

Samples collected at peak immunogenicity

- 137 stored plasma/serum samples from healthy HIVIS/TaMoVac vaccinees collected 1 month after the final vaccination (collected 2009 to 2014)

Samples collected over time

Stored serum samples from healthy HIVIS03/06 vaccinees

- 29 samples collected 1 month after 3XHIV-DNA+2XHIV-MVA
- 23 samples collected 16 months after 3XHIV-DNA+2XHIV-MVA
- 20 samples collected 3 years after 3XHIV-DNA+2XHIV-MVA

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Material and methods

ELISA (4th generation diagnostic assay)

- Enzygnost® HIV Integral 4 ELISA (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany)

Western blot

- MP Diagnostics™ HIV Blot 2.2 western blot assay (Eschwege, Germany)

Rapid diagnostic tests

- SD Bioline HIV 1/2 3.0 (Standard Diagnostic Inc, Giheung-gu, Republic of Korea)
- Determine HIV 1/2 (Alere Medical Co.Ltd, Chiba, Japan)
- UniGold HIV (Trinity Biotech, Bray, Ireland)

ELISA (in-house vaccine-specific assay)

- Subtype C rgp140 (reported as end-point titer)

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Results

VISR was common at peak immunogenicity

Reactivity in **Enzygnost® HIV Integral 4 ELISA**: 128/137 (**93%)**

Western Blot

Organization	Criteria for positive interpretation	Frequency of VISR
CDC and APHL	Presence of any two of p24, gp41, gp120/gp160 bands	136/137 (99.3%)
WHO	Presence of two ENV bands with or without GAG or POL	91/137 (66.4%)

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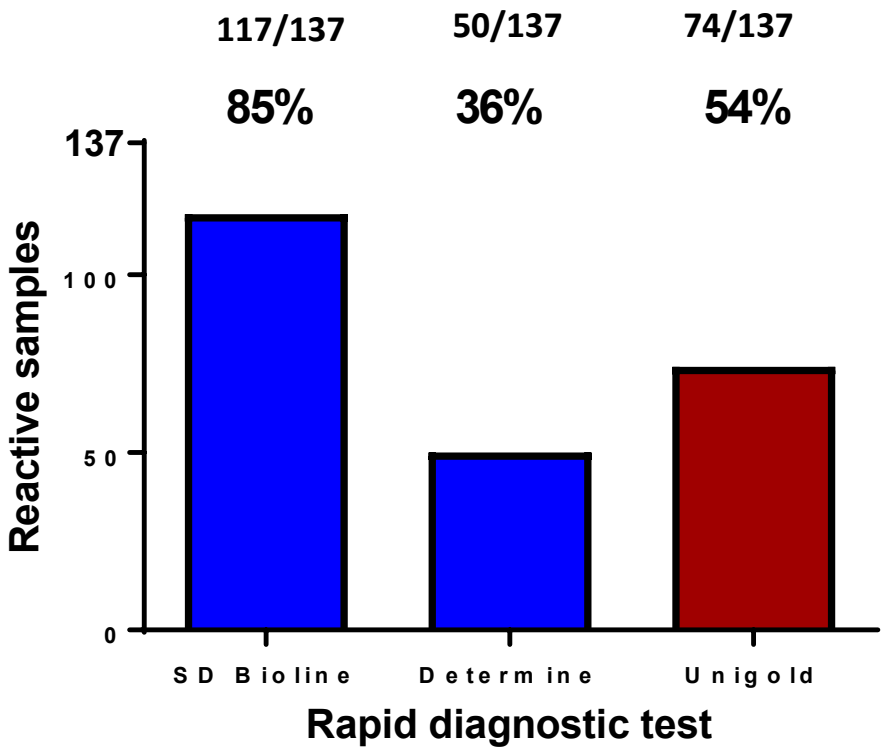
Results

VISR was common at peak immunogenicity



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Results

Missclassification by HIV diagnostic algorithm

Country	Algorithm	Rate of missclassification
Tanzania	Sequential testing SD Bioline HIV1/2, Uni-Gold™ HIV	**74/137 (54%)**
Mozambique	Sequential testing Alere Determine HIV1/2, Uni-Gold™ HIV	**36/137 (26%)***

*Significantly lower, p<0.0001

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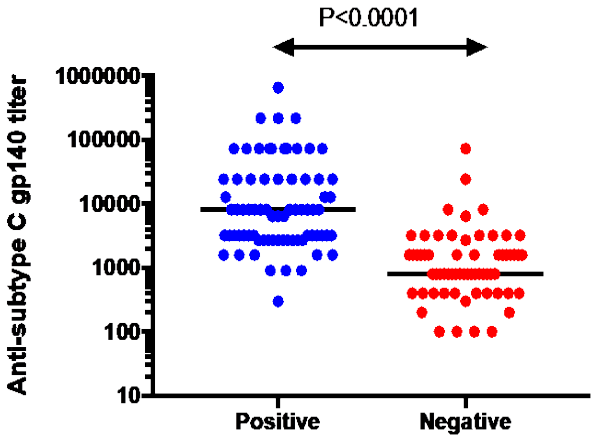
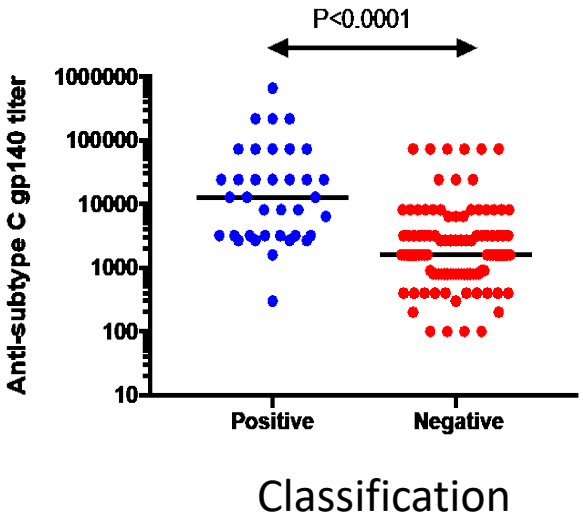
Results- antibody titers matter

(peak immunogenicity, n=137)

Tanzanian algorithm
SD Bioline HIV1/2 (screening)
UniGold™ HIV (confirmation)



Mozambican algorithm
Determine HIV1/2 (screening)
UniGold™ HIV (confirmation)



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Results

The rate of missclassification wained over time in HIVIS03/06 vaccines (3xHIV-DNA+2XHIV-MVA)

Algorithm	Number of Reactive/ Number of Tested, (%)		
	1 month after the second HIV-MVA vaccination	**16 months** after the second HIV-MVA vaccination	**3 years** after the second HIV-MVA vaccination
Tanzanian	14/29 (48)	2/23 (8.7)	0/20
Mozambican	7/29 (24)	2/23 (8.7)	0/20

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Conclusion

- The HIV diagnostic algorithms used in Tanzania and Mozambique will missclassify a substantial proportion of healthy HIV vaccine recipients

- Efforts are needed to develop simple, affordable, serological or molecular tools that can discriminate VISR from true HIV infection at the point of care.

Msafiri F et al. Vaccines **2022,** 10, 1062; doi. 10.3390/vaccines10071062

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The volunteers

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